The role of extracellular vesicles in the pathogenesis of diabetic retinopathy

Diabetic retinopathy (DR) is a major complication of diabetes mellitus (DM), and is a leading cause of blindness in working-age populations. Extracellular vesicles (EV), including small exosomes (30-150nm), are double-membrane EVs produced by almost every cell type. They carry lipids, proteins, DNAs, and RNAs that include MicroRNAs, LncRNA, and mRNA. Previous studies found that exosomes derived from mesenchymal stem cell improve DR. The purpose of this study is to investigate the role of extracellular vesicles and exosomes in the pathogenesis of diabetic retinopathy. EVs/exosomes were isolated from the culture media of primary human retinal pericytes treated with diabetes-like conditions (high glucose + TNFa/ IL6) and mannitol as osmotic control, using a differential centrifugation method. Western Blotting and Transmission Electron Microscopy characterized and validated the appropriate sizes of and marker protein presence in the EVs/exosomes. The EV/exosome's effects on the endothelial cell barrier function were evaluated by adding the isolated EVs/exosomes to retinal endothelial cell (REC) cultures and measuring the cell resistance using Electric Cell-Substrate Impedance Sensing (ECIS) and immunofluorescence. The effects of EVs/exosomes on cell viability and toxicity were measured with LDH assay. Our results showed that EVs/exosomes in diabetic conditions impair REC barrier function and cell viability. However, the EVs/exosomes in non-diabetic conditions had a protective effect, such as increased cell viability and higher cell resistance. Together the data suggest that EVs/exosomes play an important role in retinal vascular cell communications in normal physiology, but they contribute to the pathogenesis of DR in pathological conditions. Further analysis is underway to identify the specific proteins involved in EV/exosome-mediated retinal vascular cell (mis)communications. A better understanding of the roles of EVs/exosomes in retinal vascular cell function could lead to a potential clinical application to patients with DR.